UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,894	12/15/1999	MARC PIECHACZYK	19141-007	5731

7590 01/29/2003

IVOR R ELRIFI
MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1632	28

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/341,894	Piechaczyk
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *August 8 and November 6, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *32-42* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *32-42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 8, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is a 371 national stage filing of PCT/FR98/00081, filed January 16, 1998 which claims benefit to foreign application FR 97/00540, filed January 20, 1997 in France.

Applicants' amendment filed August 8, 2002, paper number 23, has been received and entered. The specification has been amended. The drawings have been entered. Claims 1, 4, 5, 11, 13, 14, 20, 21 and 31 have been canceled. Claims 32-42 have been added. Additionally, Applicants' amendment filed November 6, 2002, paper number 26, has been received and entered. The specification has been amended.

Claims 32-42 are pending.

Sequence compliance

Applicants' amendment filed November 6, 2002, paper number 26, has been entered and the raw sequence listing has been entered as paper number 27. The application is now in sequence compliance.

Specification

The disclosure objected to because of the following informalities is withdrawn.

The submission of drawings and amendments to the specification has obviated the basis of the objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Applicants review the basis of the rejection as it applied to claims 1, 4, 5, 11, 13, 14, 20, 21 and 31 and argue that the embodiment of a 'signal peptide' is fully supported by the present specification. Applicants note that at several locations in the specification a description of the biological material comprises 'elements guaranteeing.. the secretion in the blood circulation of a mammal of a therapeutically effective amount of this antibody'. Further, it is argued that signal peptides were well known at the time of filing as exemplified by the Stryer Biochemistry textbook. See Applicants' amendment, pages 8-9. Applicants' arguments have been fully considered but not found persuasive.

Newly added claim 32 recites that 'the nucleic acid comprises a sequence for termination of the transcription, situated downstream from the sequence coding for the antibody molecule and a sequence permitting the secretion of the antibody' from the mammalian non-plasmacyte

cell and claim 33 recites 'wherein the coding polynucleotide is operably linked to a polynucleotide element required for the secretion of the antibody polypeptide' from the mammalian non-plasmacyte cell. Initially, it is noted that these specific embodiments are inconsistent with the preamble which requires the nucleotide sequence code for a native unmodified antibody molecule because each are directed to modifications. In particular, this would be inconsistent with the addition of a heterologous signal peptide.

At the time of filing it was known in the art that the processing of an endogenous antibody polypeptide allows for the endocytosis of said antibody. This is supported by previous arguments where it was argued that the embodiment of a signal peptide was supported by the presence of the endogenous sequence (as demonstrated in an unlabeled figure)(paper number 20, pages 6-7). The leader sequence previously pointed to in the drawings represent sequences which are polypeptide leader sequences for post-transnational modifications and direct the translated protein into the endoplasmic reticulum. Applicant is confusing leader sequences present on antibodies as disclosed in figure 1 which direct translated polypeptides to the endoplasmic reticulum or Golgi (also see Immunology, Roit *et al.* Section 9.11, figure 9.27) with specific sequences associated with secretion into the extracellular milieu. Examiner acknowledges that signal peptides were known at the time of filing, and that these sequences could be identified in databases or by protein analysis programs, however this is not the basis of the present rejection. Knowledge in the art can not provide support for a specific element claimed, only the specification can do this. The courts have stated that "[I]t is not enough for

purposes of written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modification that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.* (Fed. Cir. March 1997) 41 USQP2d 1961 at 1966. In the instant case, the portion of the specification relied upon describes the biological material contemplated as it is directed to a nucleic acid but does not specifically describe or indicate a leader sequence (page 4, lines 17-24), and the specific recitation noted in Applicants amendment characterizes the nucleic acid as having elements guaranteeing the *in vivo* expression, but specific secretion elements or the specific location of these sequences is not set forth. Importantly, there is no description of nucleic acid sequences which are directed towards 'elements' for secretion of a protein or specific sequences which encode these sequences in the specific lines indicated by Applicants. It is noted that in preceding lines that an transcriptional element is set described as 'a termination sequence of the transcription, situated downstream from the antibody gene and permitting the secretion of the antibody gene product in the blood circulation' (as amended), however this does not support a second and separate element for the secretion of encoded antibody. Rather, it seems to state that the termination sequence is causing secretion. Examiner would agree that the specification generally supports the secretion of the translated antibody produced, however the only specific 'element' described in the present specification is a termination sequence. Further, the specification is silent with respect to description of any signal peptide which would 'permit' or which is 'required' for secretion, or the means to attach any sequence to an antibody gene.

Therefore, for the reasons above and set forth in the previous office action, the rejection is maintained.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 32-42 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described is maintained

Claims 32-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

In the instant case, the recitation of 'coding for a native, unmodified antibody molecule' is considered new matter because it extends the scope of the claims beyond that which is supported by the specification. The literal support for 'coding for a native, unmodified antibody molecule' comes from page 5, lines 5-13, which has been amended to provide a more literal translation of the French document (see paper number 23, page 2). However, this description is of a 'therapeutic antibody gene', and does not support the simple expression of any antibody gene

which is not therapeutic. This is considered new matter because it expands the scope of the claims beyond an unmodified therapeutic antibody gene as specifically recited in the specification to any unmodified antibody gene. In analyzing the specification, a 'native unmodified antibody molecule' is not specifically defined or described in the specification, however the specification in general supports the expression of a therapeutic antibody. As noted above the types of therapeutic antibodies contemplated comprise a native unmodified antibody molecule (page 5, lines 5-10) in particular, sequences which are 'recombinant antibodies retaining the properties of the original antibody' (page 11, lines 24-25). A plain interpretation of the specification and these passages indicates that the specification contemplates polynucleotide sequences encoding a therapeutic antibody, and the portion of the antibody which is encoded is not modified. The specification is silent with respect to description or example of a complete antibody gene which has not been modified, i.e. complete genomic fragment comprising an antibody gene or encoding the complete antibody molecule, and to the contrary, provides specific guidance for the alteration of known antibody sequences and their use in the generation of recombinant sequences wherein promoters and termination sequences are added to the antibody coding sequences. Thus, upon review of the specification the expression of therapeutic antibodies wherein the polynucleotide sequences encoding the antibody have not been modified is found to be supported by the specification, however the broader limitation of any unmodified antibody is not, and therefore, is considered new matter.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 32-42 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 32, 40 and 42 are unclear and confusing in the recitation of 'coding for a native, unmodified antibody molecule' because the metes and bounds encompassed by these limitations are not clearly set forth. Upon review of the specification these terms are not specifically defined, and are in contrast to the modifications of the polynucleotide sequences set forth in (a) and (b), in particular the addition of sequences which permit the secretion of the antibody. Dependent claims are included in the basis of the rejection because they fail to clarify the basis of the rejection . For example, claim 33 indicates the addition of sequences which are 'required' for secretion and claims 34 and 41 indicate that the sequences contemplated are fragments of the complete antibody molecule (as they are directed to only light and heavy chains). It is unclear if the claims only encompass complete antibody genes or if they encompass simply to using unmodified coding sequences, including fragments of the entire gene. Additionally, the claims are unclear in the recitation of 'is suitable' because the metes and bounds of the claims are subject to change depending on what one may consider a suitable characteristic for any particular or intended use. For example, a mouse cell may be suitable for implantation into a mouse, however unsuitable for implantation into a human. In this case, the claims are indefinite because they depend on a future intended use of the claimed product.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Wright *et al.*

Applicants note the amendments to the claims and the requirements of a reference for anticipation citing *Scripps clinic & Research Foundation v. Genentech Inc.* Applicants argue that Wright *et al.* does not anticipate the claims because it provides teachings for the *in vitro* production of monoclonal antibodies and that the non-lymphoid cells taught are transformed cell lines which would not be suitable for implantation and would not be maintained in a mammal for several months. See Applicants' amendment, page 11. Applicants' arguments have been fully considered but not found persuasive.

First, it is noted that claims 32-39 recite that the cell should be maintained in a mammal for several months, but that the method of making said cell, claims 40-41 do not recite this limitation and thus, arguments are not found persuasive over claims 40 and 41. With respect to claims 32-39, the ability of being maintained in a mammal would be affected by multiple factors and is directed to one potential use of the cells which are being claimed (see 35 USC 112, second paragraph rejection above). In the instant case, any cell depending on its use or means of

delivery would meet the limitation of intended use of this embodiment because the appropriate conditions would be found to maintain the cells. Furthermore, transformed cells are capable of proliferating in the form of a tumor in animal models, thus the cells of Wright *et al.* would be maintained in mammal. There is no guidance on the 'suitability' of any particular cell type which is encompassed by the instant claims and again would be dependent on an intended use. Further, it is noted that the transformed cell lines taught by Wright *et al.* are similar to those disclosed in the working examples in the instant specification. Wright *et al.* disclose non-plasmacyte cells which contain heterologous polynucleotide sequences which express and secrete an antibody (summarized in abstract). Wright *et al.* discuss the use of the antibodies for therapeutic purposes (page 125). Finally, Wright *et al.* give guidance and provide specific methods for the use of a variety of vectors and expression systems for expressing antibodies in cells which react to both viral and cancer antigens. Therefore, Wright *et al.* anticipates the claims.

Claims 32-38, 40, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson *et al.*

Applicants note the amendments to the claims and the requirements of a reference for anticipation citing *Sripps clinic & Research Foundation v. Genentech Inc.* Applicants argue that Stevenson *et al.* does not anticipate the claims because it teaches chimeric antibodies not a native

unmodified antibody as recited in the pending claims. See Applicants' amendment, page 12. Applicants' arguments have been fully considered but not found persuasive.

It is noted that the newly added claims recite 'a native unmodified molecule'. This term is not specifically defined or described in the specification however, a reasonable interpretation of this embodiment in light of the teachings of the specification is that the polynucleotide sequences encoding the antibody has not been modified. Stevenson *et al.* teach mammalian expression vectors capable of providing the expression and production of various antibodies which are secreted from the cells (see figure 1). With regard to the expression of ScFv fragments, it is noted that Stevenson *et al.* does not alter the sequences that encode portions of the antibody, leaving the native V_H and V_L regions unmodified. The antibody produced by Stevenson *et al.* therefore represents a native unmodified antibody molecule. The antigen to which the antibody reacts is directed to a tumor related epitopes (page 213). Further, the V_H1 portion of the sequence contains the leader sequence allowing for the exit of the protein from the cell (see figure 2 and legend). Since a reasonable interpretation of 'a native unmodified molecule' includes native unmodified fragments of an antibody, the vectors and cells transduced with said vectors which express an antibody as taught by Stevenson *et al.* anticipates the claims.

Claims 32-37 and 39-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen *et al.* (1994).

Applicants note the amendments to the claims and the requirements of a reference for anticipation citing *Scripps clinic & Research Foundation v. Genentech Inc.* Applicants argue that Chen *et al.* does not anticipate the claims because it teaches chimeric antibodies not a native unmodified antibody as recited in the pending claims. See Applicants' amendment, page 13. Applicants' arguments have been fully considered but not found persuasive.

It is noted that the newly added claims recite 'a native unmodified molecule', however as discussed above, this term is not specifically defined or described in the specification. However, a reasonable interpretation of this embodiment in light of the teachings of the specification is that the polynucleotide sequences encoding the antibody has not been modified. Chen *et al.* teach mammalian expression vectors capable of providing the expression and production of various antibodies which are secreted from the cells (page 5932, figure 1). With regard to the expression of Fab fragments, it is noted that Chen *et al.* does not alter the sequences that encode portions of the antibody, leaving the native V_H, C_H, C_K and V_K regions unmodified. The antibody produced by Chen *et al.* therefore represents a native unmodified antibody molecule. The antigen to which the antibody reacts is directed to a the gp120 molecule of HIV (abstract, page 5932). Further, Chen et al. teach signal leader sequences allowing for the exit of the protein from the cell (see figure 1). Since a reasonable interpretation of 'a native unmodified molecule' includes native unmodified fragments of an antibody, the vectors and cells transduced with said vectors which express an antibody as taught by Chen *et al.* anticipates the claims.

Claims 32-37 and 39- 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen *et al.* (1996).

Applicants note the amendments to the claims and the requirements of a reference for anticipation citing *Sripps clinic & Research Foundation v. Genentech Inc.* Applicants argue that Chen *et al.* does not anticipate the claims because it teaches chimeric antibodies not a native unmodified antibody as recited in the pending claims. See Applicants' amendment, page 14. Applicants' arguments have been fully considered but not found persuasive.

It is noted that the newly added claims recite 'a native unmodified molecule', however as discussed above, this term is not specifically defined or described in the specification. However, a reasonable interpretation of this embodiment in light of the teachings of the specification is that the polynucleotide sequences encoding the antibody has not been modified. Chen *et al.* teach mammalian expression vectors capable of providing the expression and production of various antibodies which are secreted from the cells (page 1517, figure 1). With regard to the expression of Fab fragments, it is noted that Chen *et al.* does not alter the sequences that encode portions of the antibody, leaving the native V_H, C_H, C_L and V_L regions unmodified. The antibody produced by Chen *et al.* therefore represents a native unmodified antibody molecule. The antigen to which the antibody reacts is directed to a the gp120 molecule of HIV (abstract, page 1515). Further, Chen *et al.* teach signal leader sequences allowing for the exit of the protein from the cell (see figure 1). Since a reasonable interpretation of 'a native unmodified molecule' includes native

unmodified fragments of an antibody, the vectors and cells transduced with said vectors which express an antibody as taught by Chen *et al.* anticipates the claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630